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Primer

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Autoimmune encephalitis

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Abstract

Autoimmune encephalitis (AE) is a treatable neuro-inflammatory disorder that is increasing in incidence. AE can be associated with malignancy (paraneoplastic), but in many patients no tumour is present. The disease presentation of AE can be heterogeneous depending on the type of antibody involved. AE is often caused by neuronal antibodies that bind to extracellular autoantigens (that is, *N*-methyl-D-aspartate receptor (NMDAR) and LGI1). Binding of these antibodies causes dysfunction of synaptic receptors, which leads to neurological symptoms. In these patients, treatment with immunosuppressive therapies is believed to decrease inflammation and deplete antibodies, and is essential for recovery. AE can also occur in patients with antibodies against intracellular antigens (such as Hu and Ri), often in the setting of malignancy. In these patients, tumour treatment is essential for stabilization or improvement. The most frequent symptoms of AE are cognitive problems, behavioural changes and seizures. Rapid recognition of AE syndromes is essential as earlier treatment of AE leads to better outcomes. For a definite diagnosis, the identification of an autoantibody is essential; however, some patients have seronegative AE. Most patients are severely affected during the acute disease stage, but long-term functional recovery is often good, particularly for patients without cancer. Nevertheless, residual anxiety, fatigue and cognitive problems can considerably affect quality of life. Research focuses on improving the understanding of pathophysiological processes, establishing patient-tailored outcome measures, optimizing treatment prediction models and studying different therapeutic regimens, all aiming to improve treatment and long-term outcomes.

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Introduction

Autoimmune encephalitis (AE) is a neuro-inflammatory disease that causes progressive inflammation of the brain. AE is often characterized by the presence of neuronal autoantibodies, for example, anti-*N*-methyl-D-aspartate receptor (anti-NMDAR), anti-LGI1, anti-GAD65 and anti-Hu[1]. AE can be paraneoplastic, but in many patients with AE no tumour is present, and in those patients the aetiology is probably multifactorial. Other less common causal factors are recent herpes simplex virus 1 (HSV1) encephalitis[2] and the use of immune checkpoint inhibitors for the treatment of cancer[3]. Studies have identified >15 neuronal antibodies that cause AE and have described their related syndromes in detail[3]. The description of clinical syndromes has improved awareness, which is also reflected by an increase in the prevalence of AE. In most cases, AE manifests as limbic encephalitis, although it can affect all regions of the brain. Conventionally, AE was considered only in the diagnostic work-up of severely ill patients with a subacute onset of cognitive problems, often combined with psychiatric symptoms and refractory seizures or status epilepticus[4–7]. Studies have demonstrated that not all patients develop severe limbic encephalitis or pan-encephalitis, and that patients can also have prolonged disease courses with less prominent symptoms[8–12]. For instance, in anti-LGI1 encephalitis, most patients gradually develop focal seizures together with or without facio-brachial dystonic seizures, followed by cognitive impairment and focal to bilateral tonic-clonic seizures[9,13,14]. Research over the past decade has focused on earlier recognition of symptoms, making diagnosis more uniform. As a result, diagnostic guidelines were published in 2016, which has been a major step forwards in the field[12]. In antibody-negative patients, the criteria established to diagnose 'probable seronegative AE' have been very useful[15]. In addition, the criteria for 'probable anti-NMDAR encephalitis' have facilitated earlier immunotherapy in those with high suspicion of this form of AE. Other factors that aim to facilitate earlier and better AE diagnosis are the availability of different diagnostic prediction tools, including the Paraneoplastic Neurological Syndromes (PNS) Care score[16] and optimization and better interpretation of different laboratory techniques. Despite such progress, underdiagnosis and misdiagnosis are common in the field of AE. An increased knowledge of the pathophysiology and a better awareness of disease symptoms are warranted to decrease both in the near future. Concerning AE treatment, the first randomized trial evaluating the efficacy of immunotherapy has been published[17] and several trials are recruiting or are in development. These trials, as well as other types of research to assess treatment effects, will make a key contribution to the standardization of treatment regimens. These steps are essential for precision medicine in the future, comparing different treatments using patient-specific characteristics from multiple countries and cohorts, necessary in rare diseases such as AE. In addition, all efforts share the goal of accelerating functional recovery in patients and improve long-term cognitive outcomes.

In this Primer, we describe the epidemiology, pathophysiological mechanisms, current diagnostic process, treatment, prognosis, quality of life and future perspectives of AE, focusing on adult patients.

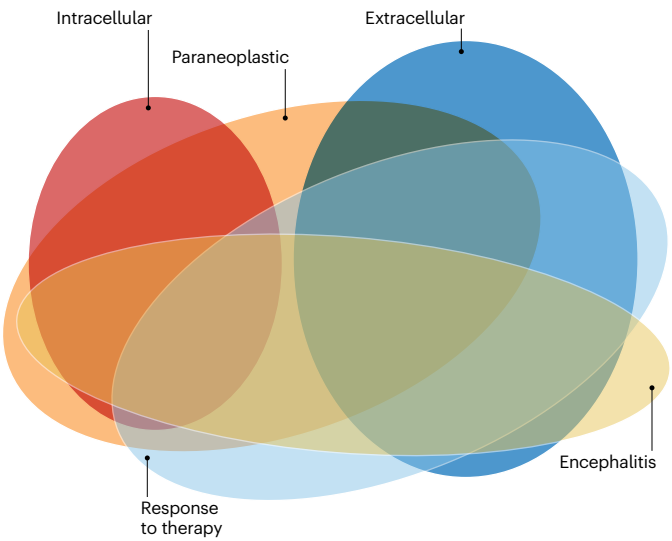

Fig. 1 | Overlap of antibody types causing or associated with autoimmune encephalitis. The overlap and differences between autoantibodies against intracellular (red) and extracellular (blue) antigens are demonstrated. Patients with antibodies against intracellular epitopes often have a paraneoplastic aetiology of symptoms, but tumours can trigger both type of antibodies. All cell types in the brain can harbour antigens that are recognized by autoantibodies and therefore all types of brain inflammation can occur. Encephalitis (limbic encephalitis or pan-encephalitis) is associated most, but not exclusively, with patients who have autoantibodies against extracellular antigens. As autoantibodies against intracellular antigens generally are not pathogenic, and damage is more easily inflicted, these patients have a lower chance to recover from symptoms after immunotherapy than those with autoantibodies against extracellular targets.

Epidemiology

Definition and incidence

AE is an umbrella term that includes specific biomarker-defined variants with clear published case definitions (for example, anti-NMDAR encephalitis) and variants of exclusion (probable seronegative AE). AE comprises patients with an autoimmune aetiology and patients with a paraneoplastic aetiology (Fig. 1). AE is a rare disease with an estimated cumulative incidence of 0.5–1 per 100,000 persons per year (Table 1) in adults and between 1.0 and 1.3 per 100.000 persons per year in children. The incidence of AE in children is mainly driven by an increased incidence of anti-NMDAR encephalitis and acute disseminated encephalomyelitis (ADEM). The described incidence varies because of evolving disease concepts, selection bias in the available cohorts and incomplete case registrations[12].

Although cohort studies describing overall incidence initially included ADEM (often associated with myelin oligodendrocyte glycoprotein (MOG) antibodies)[12], generally ADEM, glial autoimmune syndromes (that is, other MOG antibody associated diseases (MOGAD))[18] or neuromyelitis optica spectrum disease (NMOSD)[19] are considered acute demyelinating syndromes and not classified under AE[18–20]. Other neuronal antibody associated syndromes, such as stiff-person syndrome, are not included in AE incidence calculations although these conditions can have phenotypic and serologic overlap with AE[21]. AE sequelae that affect up to 25% of young patients following HSV1 encephalitis are considered part of the AE spectrum[22]. Encephalitis syndromes with an infectious, metabolic or toxic cause, and encephalitis associated with systemic conditions (for example, neurosarcoidosis) are not included in the definition of AE[12].

The introduction of immune therapies, collectively referred to as immune checkpoint inhibitors, in cancer treatment has led to various immune-related adverse events in 1–3% of treated patients[23,24] and <50% of these individuals have AE (with or without detectable autoantibodies). As these therapies are increasingly being approved for different

Table 1 | Reported incidence rates for common AE variants

Population	Study years	Cohort	Region	Estimated incidence rate *n* per 100,000 persons per year (95% CI)	Ref.
Anti-NMDA receptor encephalitis					
All age groups	1995–2016	Regional, population based	North USA	0.03[a]	204
	2013–2018	Regional, referral/centre based	Trento and Treviso, Italy	0.04 (0.01–0.13)	205
	2005–2006	Hospital based	England	0.09	206
	2016–2018	National, referral laboratory based[b]	France	0.09 (0.04–0.16)[b]	207
	2007–2019	National, laboratory/referral based	The Netherlands	0.1[c] (0.062–0.159)	7
	2009–2018[d]	National, population based	Denmark	0.17[d]	208
	2011–2022	Regional	Southern California	Black, 0.29 (0.13–0.46); Hispanic, 0.22 (0.15–0.28); Asian/Pacific Island, 0.20 (0.08–0.33); white, 0.04 (0.01–0.07)	36
	2015–2019	Regional, hospital based	Saba, Malaysia	Overall, 0.23; adult, Austronesian, 0.26 and Chinese, 0.13; paediatric, Austronesian, 0.36 and Chinese, 0.26	209
Paediatric patients	2011–2017	National, population based	Denmark	0.07	210
	2010–2011	National, survey-surveillance study	UK	0.09 (0.06–0.11)	211
	2008–2015	National, hospital based	New Zealand	Non-Māori, 0.02 (0.0–0.1); Māori, 0.34 (0.14–0.7); Pacific descent, 1.0 (0.4–2.0)	37
	2009–2015	Regional, hospital based	Hong Kong	0.22 (0.12–0.36)	212
Anti-LGI1 encephalitis					
Adults[e]	2016–2018	National, referral laboratory based[b]	France	0.06 (0.02–0.13)[b]	207
	2007–2015	National, referral laboratory based	The Netherlands	0.08	13
	2013–2018	Regional, referral centre based	Trento and Treviso, Italy	0.1 (0.05–0.23)	205
	2009–2018	National, hospital based	New Zealand	0.14	213
AE (overall)[f]					
All age groups	2016–2021	National, referral laboratory based	The Netherlands	0.56 (0.52–0.61)	
	2016–2018	National, referral laboratory based	France	0.32 (0.29–0.34)	207
	1995–2015	Regional, laboratory based	Minnesota, USA	0.8	204
	2009–2017	Regional, laboratory based	Northeastern Italy	0.89	214
Adults	1987–2018	Regional, laboratory based	Minnesota, USA	0.6	215
Paediatric patients	2015–2018	National, referral laboratory based	The Netherlands	0.15 (0.1–0.24)	25

AE, autoimmune encephalitis; NMDAR, *N*-methyl-D-aspartate receptor. [a]The incidence rate is based on the entire observational interval from 1995 to 2016. The authors indicate an increase in antibody-positive AE from 0.1 to 0.6 in 2006–2015 compared with 1995–2005, probably due to increased awareness. However, incidence rate changes for anti-NMDAR encephalitis in particular are not provided. The indicated incidence rate is probably underestimated. [b]The incidence rate in the final year of observation 2018 is indicated. Incidence rate increased in previous years. [c]Across the entire recruitment interval. The incidence rate peak in 2017 is 0.15 (0.099–0.22). [d]The incidence rate in the final year of observation 2018 is indicated. Incidence rate increased in previous years. [e]Adults were defined as age >15 years[213]. [f]Including antibody-positive AE (and paraneoplastic) and seronegative AE, excluding acute disseminated encephalomyelitis.

cancers, the incidence of an immune-related adverse event is likely to increase and will become a large part of the total amount of AE cases.

Considering the rarity of AE, incidence data are mostly derived from large cohorts recruited by expert centres specialized in autoantibody testing (Table 1). Often, there is considerable selection bias and coverage is mostly incomplete. Population-based cohorts in small countries or regions are limited by the final case numbers in rare disease. Unfortunately, national health-care databases are currently not well suited to evaluate the incidence of AE. The international classification of diseases, tenth revision (ICD-10) does not specifically categorize AE, and the more comprehensive OrphaNet coding is not universally applied in most countries. Despite these methodological differences, incidence values across studies show very good concordance (Table 1).

Demographics

The sex and age of individuals varies considerably within AE variants (Fig. 2). Strong female predominance is observed in adult-onset teratoma-associated anti-NMDAR encephalitis[5] and male predominance is observed in anti-CASPR2 encephalitis and in anti-LGI1 encephalitis (~60%)[8,13]; however, in other variants, both sexes are equally affected (Fig. 2). AE occurs in children, adolescents and adults of all ages, yet each age group has specific spectra of causative AE variants (Fig. 2). Most paediatric patients with antibody-positive AE have NMDAR or MOG antibodies[22,25,26]. By contrast, older adults rarely have ADEM with MOG antibodies, and CASPR2 antibodies are mainly found in men >65 years of age. Older adults, often with a history of smoking, more often have underlying small cell lung cancer (SCLC)[16]. Of note, some AE variants

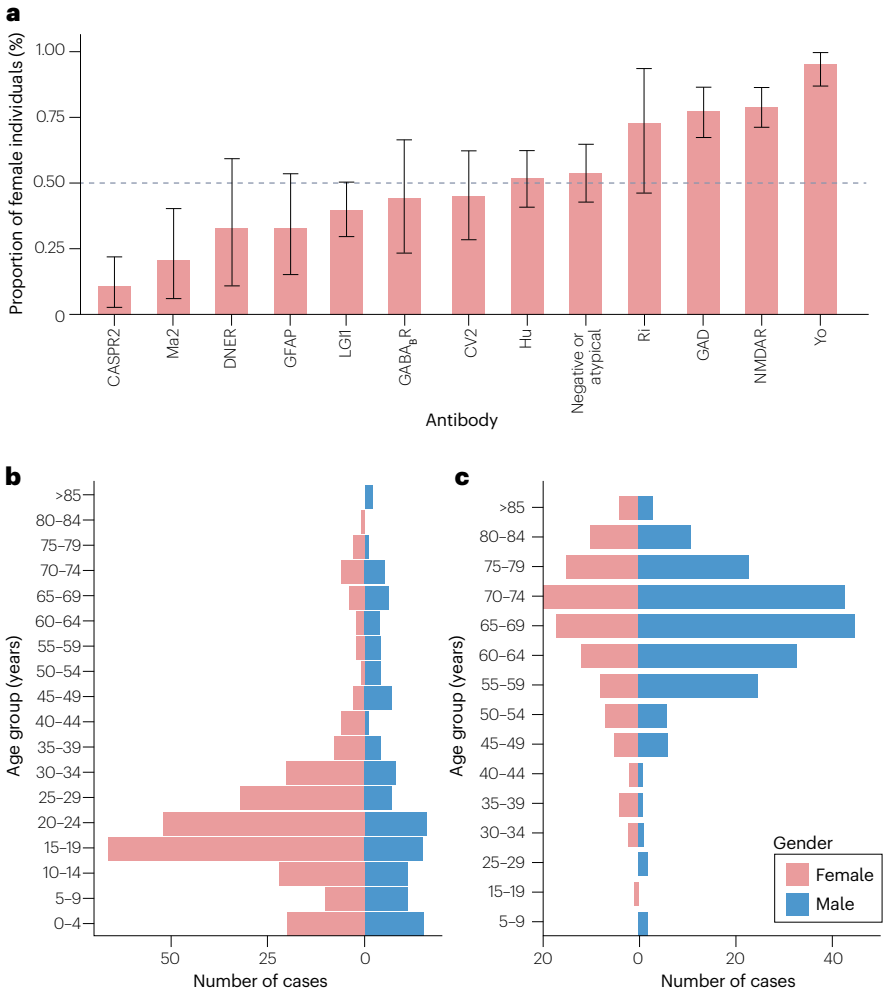

Fig. 2 | Demographics of autoimmune encephalitis variants. a, The percentage of female individuals (women and children) with different types of autoimmune encephalitis[207]. **b**, The age distribution for anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. **c**, The age distribution of anti-LGI1 encephalitis, combining the data from two nationwide cohorts in western Europe[41,207]. Anti-NMDAR encephalitis occurs mostly in young females, whereas anti-LGI1 encephalitis occurs mostly in middle-aged patients and is slightly more common in men than in women[41]. $GABA_BR$, $GABA_B$ receptor. Part **a** reprinted with permission from ref. 207, Wolters Kluer.

have a bimodal age distribution, with important differences in tumour associations. For example, rare anti-AMPAR encephalitis can be seen in young and middle-aged adults with thymoma, but is more frequently idiopathic in young adults. In older patients, the disease more often has a paraneoplastic aetiology (breast or lung cancer)[27].

Risk factors

The main reported risk factors in certain AE variants are underlying tumours of neuroectodermal origin, neuroendocrine origin or lymphoma (paraneoplastic); the presence of certain heterozygous or homozygous HLA haplotypes[28–30]; prior use of immune checkpoint inhibitors; and recent episodes of viral encephalitis. Specifically, in 25% of patients with the latest HSV1 infection, anti-NMDAR encephalitis occurs with an interval of 3–8 weeks, and AE has also been described following an episode of Japanese encephalitis[31]. A seasonal variance seems to be present in NMDAR, with a summer and autumn predominance of clinical onset, although the causative risk factors are unknown.

Genetic risk factors. In some AE variants, a strong genetic predisposition exists. Almost 85–90% of patients with anti-LGI1 encephalitis carry the *HLA-DRB1*07:01* allele[28,29,32] and homozygosity confers a doubling of risk[33]. However, ~12–27% of the healthy population carries this HLA haplotype[29,32]. What constitutes the probable second factor is currently unknown; cross-reacting microbial peptides in susceptible individuals is just one hypothesis. Furthermore, not all AE variants have an HLA-based predisposition. Indeed, >50% of anti-NMDAR encephalitis cases[5] and almost all MOG encephalitis cases[34] occur in children and young adults without any of these trigger factors and without strong HLA associations[32,35].

Geographical heterogeneity

Most available epidemiological studies include patients with anti-NMDAR encephalitis, with a reported incidence ranging from 0.09 to 0.26 per 100,000 individuals per year (Table 1).

The incidence is 4–7-fold higher in countries with Black, Asian or Hispanic individuals than in regions with mainly white individuals[5,36]. In New Zealand, the incidence is higher among Pacific Islander or Maori children than non-Indigenous populations[37]. Interestingly, in China, anti-NMDAR encephalitis was more frequent in men whereas anti-NMDAR had a female predominance elsewhere, showed a milder disease course, less intensive care unit admission, was less frequently associated with ovarian teratomas and showed a different HLA association[38–40].

For another common variant, anti-LGI1 encephalitis, studies have reported an incidence that is ~50% of the incidence of anti-NMDAR

encephalitis (0.6–1.4 per million individuals), and was rarely found in Black individuals[14]. However, one study (mainly including white patients) reported an incidence comparable to anti-NMDAR encephalitis[41]. Interestingly, the incidence of anti-LGI1 encephalitis is considerably lower in Japan than the rest of the world, and the aetiology is mainly paraneoplastic (thymoma), probably as the *HLA-DRB1*07:01* allele observed in 85–90% of idiopathic cases[28–30] hardly occurs in this country[42].

Mechanisms/pathophysiology

In general, AE is caused by misguided adaptive, antigen-specific immune reactions targeting the central nervous system (CNS). This general concept can be dissected into four, stepwise, partially overlapping and interacting pathogenic processes (Fig. 3). First, one or a combination of co-occurring trigger factors results in a breach of immunological tolerance. Second, the autoantigen-specific immune reaction is initiated and antigen-specific lymphocytes are recruited to the target tissue. Then, specific autoantigen-targeted immune reactions occur in the CNS, where synaptic function is affected, leading to network disruptions. The type of target antigen and its functional, anatomical and subcellular localization determines the disease manifestations. Understanding these mechanisms, and their relative dominance in each syndrome, provides a rationale to tailor treatments. Broadly, diseases mediated via $CD8^+$ T cell tissue injury, particularly those associated with antibodies to intracellular epitopes, require different therapeutic considerations than those where autoantibodies target extracellular epitopes and are considered pathogenic[43].

Breach of tolerance and autoimmunity

The best-studied trigger factors for AE are often small and occult tumours with ectopic expression of neuronal or synaptic autoantigens[16]. One common tumour entity is SCLC[44]. In this situation, immune reactions against tumour-specific antigens are part of the natural antitumour response. However, some of these antigens are ectopically expressed neuronal 'self'-antigens (onconeural antigens, such as HuD in anti-Hu syndrome). Although these onconeural immune reactions are beneficial for tumour defence, they are detrimental to the CNS and sometimes the peripheral nervous system. Onconeural autoimmunity only very rarely occurs without underlying tumours[45]. Indeed, tumour removal, to eliminate the ongoing presentation of self-antigens, is still the most potent therapeutic intervention, confirming the dominant effect of this factor. However, not all associated tumours are necessarily malignant and up to 35% of patients with anti-NMDAR encephalitis have underlying benign cystic ovarian teratomas[5]. These teratomas express NMDARs and show a dense infiltration of T lymphocytes, B lymphocytes and plasma cells, and the intratumoural B cells show NMDAR reactivity[46,47], indicating ongoing antitumour immune responses, which lead to the development of NMDA receptor-specific autoimmunity[48].

Nevertheless, why some patients with tumours develop paraneoplastic neurological syndromes and some do not, has yet to be understood. Host-specific factors (hereditary and acquired) and tumour-specific factors have been hypothesized to be involved in the pathophysiology. Host-specific factors include a weak association with specific HLA haplotypes[49] and peculiarities of central and peripheral tolerization of onconeural autoantigens in the thymus[50]. Tumour-specific factors are expression levels or mutations of onconeural antigens[51] and modulation of tumour–immune interactions[52] with the presence or absence of tertiary lymphoid-like structures in the tumour tissue[53]. Indeed, similar tumours display strong interindividual heterogeneity in the inflammatory response observed within the tumour (immunotypes)[54]. Both host factors and tumour-related factors interact in a cancer–immunity cycle[54], resulting in a T cell-promoting inflammatory tumour microenvironment. Differences in this interaction between patients could explain why some develop paraneoplastic neurological syndromes and others do not. However, the specific mechanisms shaping the antitumour immunity leading to paraneoplastic immune complications are not well understood.

Further insights into the underlying mechanisms of AE stem from two clinical observations — post-infectious encephalitis-associated CNS autoimmunity and tumour immune therapy-associated AE[22–24,31]. Up to 25% of patients with HSV1 encephalitis eventually develop symptomatic secondary AE targeting the NMDA receptors and/or other neuronal antigens[31], and demonstrated increased expression levels of type 1 interferon-related genes. Viral replication in neurons generates pathogen-associated molecular patterns (for example, double-stranded RNA), which activate pattern recognition danger receptors (such as Toll-like receptor 4) and leads to the production of antiviral type 1 interferons[31]. These interferons are potent activators of antigen presentation and expression of T cell co-stimulatory signals[55], suggesting that combining neuronal tissue destruction (virus mediated) with potent co-stimulatory T cell signalling is sufficient for breaching endogenous tolerance to neuronal self-antigens. Nonetheless, not only co-stimulation but also the absence of co-inhibition of T cells can result in autoimmunization. With the advent of pharmacological blockade of co-inhibitory signalling (that is, immune checkpoint inhibitors) to enhance endogenous antitumour immunity, it is clear that autoimmunity is a common complication. Indeed, ~1% of patients develop AE. In most patients, however, neither tumours nor the preceding viral encephalitis can be identified as triggers, suggesting that most cases are idiopathic AE. Interestingly, B cell checkpoints, those that maintain central and peripheral tolerance[56], have been investigated as points of failure in disease versus health[57]. Indeed, CASPR2-reactive naive B cells have been identified in equal proportions in health and disease, yet CASPR2-reactive memory B cells are only found in disease. Thus, defective peripheral tolerance in patients might permit licensing of pathogenic CASPR2-reactive antibodies. Ongoing efforts aim to delineate key checkpoints that may control antigen-specific tolerance.

Autoimmunity propagation and blood–brain barrier crossing

Following this initial breach of tolerance, systemic components of the immune system are needed to propagate the adaptive immune response observed in AE. Evidence shows that regional secondary lymphoid organs (lymph nodes) might be involved[46,58]. Indeed, it is only within the lymph nodes that the necessary constituents for propagation of CNS autoimmunity are found in close proximity — soluble autoantigens from the brain via g-lymphatic pathways, antigen-presenting dendritic cells, activated antigen-experienced T lymphocytes and mature B lymphocytes converge in lymphoid follicles or germinal centres. Studies have shown that germinal centres in lymph nodes in NMDAR encephalitis[46,59] and AQP4 neuromyelitis optica[58] contain affinity-matured B lymphocytes, which produce autoantibodies targeting the respective antigens. Similar constituents are present in tumour-draining lymph nodes (for example, SCLC and mediastinal lymph nodes, and teratoma and pelvic lymph nodes) where the presentation of the antigen to the immunological system occurs. This spatial convergence has been shown to promote the process of affinity maturation, inducing point mutations in hypervariable regions of the B cell receptor (that is, somatic hypermutation). Indeed, recombinant autoantibodies derived from patients

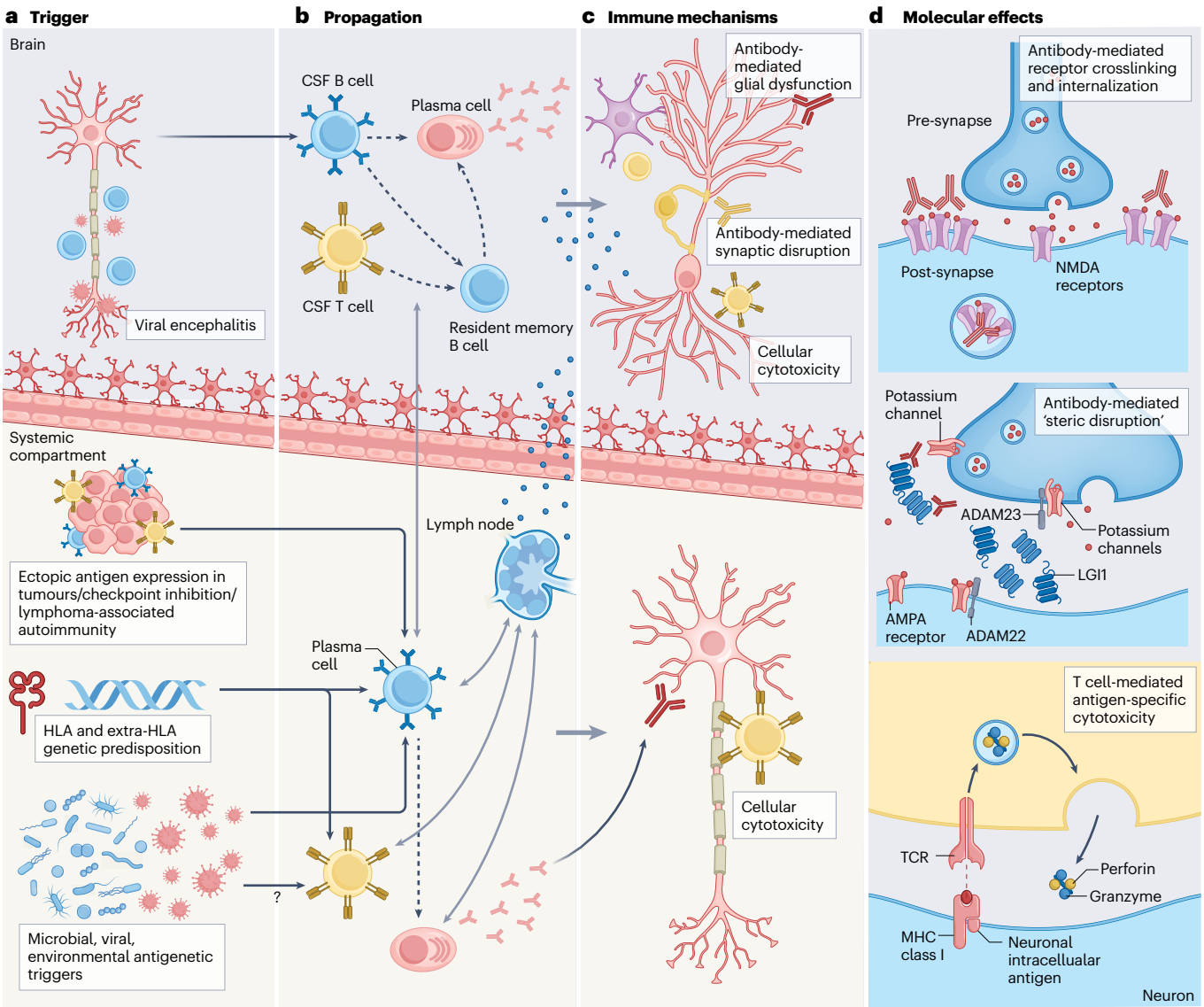

Fig. 3 | Pathogenesis of autoimmune encephalitis. a, The initial breach of tolerance caused by different and sometimes interacting triggers. Currently, these factors encompass ectopic expression of autoantigen on tumours, viral encephalitis-mediated brain tissue destruction leading to expression of autoantigens together with pro-inflammatory signals, genetic predisposition mainly caused by certain human leukocyte antigen (HLA) haplotypes and the dysfunction of immune checkpoints (iatrogenic through antitumour medication, acquired in lymphoma or hereditary immune checkpoint dysfunction). **b**, The propagation of the cellular immune reaction in the systemic compartment and development of clonally expanded antigen-specific T cells, B cells and plasma cells. Intrinsic autoantigen-specific factors (subcellular localization, tissue expression and shedding), the type and inflammatory context (tumour or virus) of the interaction and host-specific factors (HLA receptor and T cell receptor repertoire) determine this autoantigen-specific immune response. In most situations, this process initially occurs in the systemic immune compartment (most likely the lymph nodes close to the trigger, such as tumour-draining lymph nodes, or cervical lymph nodes for herpes simplex encephalitis). Eventually, autoantigen-specific lymphocytes cross the blood–brain barrier and establish themselves intrathecally. **c**, The dominant effector mechanisms on the target tissue can be broadly categorized into antibody-mediated humoral versus cellular-mediated cytotoxic (with several further distinctions) mechanisms. These categories associate with inherent differences in cytotoxicity, reversibility and response to some immunotherapies. **d**, The final step is the direct effect on neuronal/synaptic function via antibody-mediated crosslinking and internalization (top panel), steric interference with protein–protein interactions (middle panel), interference with the surface dynamics of targeted receptors (for example, *N*-methyl-D-aspartate (NMDA) receptor, not shown), disruption of intracellular scaffolding proteins or cytoskeleton (for example, IgLON5, not shown), or direct T cell-mediated cytotoxicity (lower panel)[48]. This causes synaptic dysfunction, compensatory mechanisms, network disruption and ultimately neurological symptoms. These are often reminiscent of symptoms observed in patients treated with pharmacologic antagonists of the specific synaptic protein. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CSF, cerebrospinal fluid; MHC major histocompatibility complex; TCR, T cell receptor.

with anti-LGI1 encephalitis[60] and anti-CASPR2 encephalitis[59,61] or clonally expanded intrathecal plasma cells from patients with anti-NMDAR encephalitis[62] show strong somatic hypermutation, supporting this theory[59,61,62]. Most likely, the regional draining lymph nodes involved in teratoma-associated anti-NMDAR encephalitis are mediastinal and, in HSV1 encephalitis, cervical.

Although the role of $CD8^+$ T cells in AE with intracellular antigens is mostly undisputed, some evidence exists for the involvement (or absence) of $CD4^+$ T lymphocytes in the propagation of the immune reaction in other AE variants[59]. For anti-NMDAR encephalitis, a genome-wide association study identified an association with a gene involved in T cell-independent B cell activation[35]. Nevertheless, in several late-onset AE variants (for example, *LGI1*, *CASPR2* and *IgLON5*) a strong linkage of certain HLA class II haplotypes is observed (see above). Furthermore, the occurrence of IgG4 isotype autoantibodies strongly indicates the involvement of $CD4^+$ T cells[10,63,64]. Indeed, both IgG4 class switching and affinity maturation are $CD4^+$ T cell dependent, and studies have provided some evidence of both, together with clonally restricted $CD4^+$ (and also $CD8^+$) T cells in the cerebrospinal fluid (CSF) of patients with anti-LGI1 encephalitis and anti-CASPR2 encephalitis[59]. Thus, $CD4^+$ T lymphocytes may play a part in promoting autoimmunity in some of these AE variants. Some evidence also points to the role of non-conventional T cells, namely mucosa-associated invariant T cells, in propagating this immune response[59].

The next step in the pathogenic chain of events in the development of AE is the trafficking of autoantigen-specific lymphocytes across the blood–brain barrier, to proliferate and to survive in the CNS. The hallmark of AE is the predominant infiltration of B cells and, to a lesser degree, T lymphocytes surrounding the cerebral vessels in the Virchow–Robin spaces[65], which also frequently contain plasmablasts[66] and plasma cells[67]. Fittingly, CXCL13, a strong B cell attractant, can be found in the CSF of patients with acute NMDAR encephalitis[68]. However, the source of CXCL13 in the CNS is currently unknown. In addition, the frequent (~50%)[5] prodromal symptoms observed in anti-NMDAR and other AEs are hypothesized to represent inflammatory episodes initiating this B cell attraction and propagation of antibody-secreting B cells into the CNS. However, ectopic, lymphfollicle-like structures (as observed in the meninges of patients with secondary progressive multiple sclerosis)[69] have not been demonstrated in patients with AE. Nevertheless, it is plausible that the meninges — as an immunologically active organ barrier — play a part in shaping the immune response via their capacity for negative selection of autoreactive B cells[70], which might be dysfunctional in AE.

Components of the immune reaction

One of the best-studied factors influencing pathogenicity, reversibility and prognosis is the subcellular localization of the autoantigen[1] — intracellular versus cell membrane localized (neuronal surface). Intracellular onconeural autoantigens are mostly observed in patients with malignant neuroendocrine tumours. Hu-specific T cells are present in the CSF of these patients[71], and evidence from human histopathology points towards a cytotoxic T cell-mediated process[72,73]. Even though highly specific autoantibodies are present in high titres in the serum and CSF of patients with Hu antibodies[74], they do not reach and bind their intracellular target antigen within intact cells or cause neuronal damage in vitro[75] or in vivo[76]. Yet the autoantibodies against intracellular antigens are extremely useful biomarkers. By contrast, patients with autoantigens localized on the neuronal surface (for example, NMDA receptors, CASPR2 and so on) with or without underlying tumours often have better responses to therapy as well as outcomes and prognosis[5,77]. In these patients, neuropathological studies do not provide clear evidence of cytotoxic mechanisms[65]. Instead, the autoantibodies in vitro[4] and in vivo[78] bind their target antigen in intact cells and influence its function (see 'Synaptic pathology and network effects' section). The B cell epitopes are highly conformational, and some AE variants with neuronal surface or extracellular autoantigens (for example, *LGI1* (ref. 79), *CASPR2* (refs. 80,81) and *IgLON5* (ref. 82)) show prominent IgG4 isotype autoantibodies. This peculiar antibody isotype is observed in situations of chronic antigen exposure, such as allergen tolerization[83]. IgG4 antibodies are hardly able to activate complement and can be functionally monovalent[84], reducing their crosslinking capacity. The immunological cause and functional effects of this observation for pathogenicity are still unclear but investigations in myasthenia gravis suggest that monovalency increases pathogenicity[85]. Finally, an evolving branch of research in AE and autoimmunity in general addresses the role of post-translational modifications (for example, glycosylation and so on) of the constant region of the antibodies (Fc terminus), which modify the crosstalk between different components of innate immunity such as antibody-dependent phagocytosis (by monocytes, neutrophils or microglia), antibody-dependent cellular cytotoxicity (by natural killer cells) or antibody-dependent complement toxicity. In MOGAD, some evidence points towards a relevant role of post-translational modification[86].

Synaptic pathology and network effects

Behavioural, epileptic and encephalopathic symptoms in AE are the result of synaptic, neuronal and network dysfunction. AE associated with autoantibodies targeting intracellular antigens (for example, anti-Hu syndrome) is caused by cytotoxic T cell-mediated destruction of synapses and neurons (Fig. 3). The discovery of neuronal surface autoantibodies has given rise to a new concept in neuroimmunology — autoantibodies that can directly and reversibly modulate synaptic function, thereby leading to behavioural, cognitive, movement dysfunction and epileptic seizures. This concept is strikingly different from classical antibody effector functions (that is, complement, antibody-dependent cytotoxicity). Several studies have addressed the question of how these antibodies affect the synapses, conveyed using several different in vitro and in vivo models and approaches (Table 2 and supplementary Table 1). Some antibodies (for example, NMDAR antibodies) have crosslinking abilities, causing multimeric receptor rafts and the breakdown of signalling, trafficking and intracellular scaffolding. Ultimately, internalization and degradation of these dysfunctional complexes lead to a net loss of surface receptor density. Whether this directly (primarily) occurs at the synapse or initially at better-accessible juxta-synaptic sites with secondary synaptopathy is an ongoing scientific debate[87]. Another mechanism, for example, in anti-LGI1 encephalitis, is steric interference with scaffolding proteins (Fig. 3), which results in the breakdown of the synaptic architecture and net loss of receptors and channels (via diffusion out of the synapse)[80]. Furthermore, these mechanisms can co-occur — in anti-NMDAR encephalitis, crosslinking-mediated internalization of the NMDAR, interference with its surface dynamics[88] and disruption of the crosstalk with other synaptic partners (ephrinB2 receptor and dopamine receptor) participate in the pathogenesis[89,90]. Similarly, autoantibodies against LGI1, which target distinct epitopes on the same molecule, may have different pathogenic roles[91]. In addition, direct effects of the autoantibodies on the electrophysiological properties of single receptors also play a role. Synaptic G protein-coupled receptors (for example, the $GABA_B$ receptor and mGluR5) are directly

Table 2 | The spectrum of antibodies in autoimmune encephalitis

Antigen	Neurological phenotype	Systemic tumour	Antibody assay[a,b]
Hu	Limbic encephalitis, encephalomyelitis, sensory polyneuropathy	85%, SCLC, neuroendocrine tumours	IB–IF
Yo	Paraneoplastic cerebellar degeneration	>90%, ovary, breast	IB–IF
Ma1	Limbic encephalitis, brainstem encephalitis, cerebellar degeneration	>75%, testicular (Ma2, young); lung, breast, gastrointestinal (Ma1, older age)	IB–IF
Ma2	Brainstem encephalitis, limbic encephalitis		
CRMP5 (CV2)	Encephalomyelitis, sensorimotor polyneuropathy	>80%, SCLC, thymoma	IB–IF
Amphiphysin	Stiff-person syndrome, limbic encephalitis, myelitis, polyneuropathy, PERM	80%, breast, SCLC, stomach	IB–IF
Ri	Opsoclonus-myoclonus, brainstem encephalitis	>70%, breast, lung, ovary	IB–IF
Tr (DNER)	Cerebellar dysfunction	>70%, Hodgkin lymphoma	IB–IF, CBA[c]
Kelch-like 11 (KLHL11)	Brainstem encephalitis, cerebellar ataxia, hearing loss, limbic encephalitis	~70%, germ cell tumour	CBA (CSF)
NMDAR	Psychosis, memory loss, language dysfunction, dyskinesia, autonomic dysfunction, central hypoventilation, sleep alterations (insomnia in acute stage, hypersomnia in post-acute stage)	~40% teratoma in female, mainly 12–45; ~25% carcinomas in patients >45 years	CBA (CSF more sensitive than serum)
LGI1	Limbic encephalitis, facio-brachial dystonic seizures[d]	<5%, thymoma	CBA (serum more sensitive than CSF)
CASPR2	Encephalitis, Morvan syndrome	~50% in Morvan syndrome (~25% in other phenotypes), thymoma	CBA (both CSF and serum)
$GABA_B$ receptor	Limbic encephalitis, prominent seizures	>50%, SCLC	CBA (CSF more sensitive than serum)
$GABA_A$ receptor	Encephalitis with prominent seizures, status epilepticus; very rare stiff-person syndrome	<10%, Hodgkin lymphoma, thymoma	CBA (CSF more sensitive than serum)
AMPAR (GluR1/2)	Limbic encephalitis	~65%, lung, breast, thymoma	CBA (CSF more sensitive than serum)
Glycine receptor (GlyR)	PERM, stiff-person syndrome	<10%, thymoma, Hodgkin lymphoma	CBA (both serum and CSF)
mGluR5	Encephalitis, confusion, psychiatric and memory deficits	~50%, Hodgkin lymphoma	CBA (CSF more sensitive than serum)
DPPX	Encephalitis with hyperekplexia, rare PERM-like symptoms; prodromal weight loss and diarrhoea	<10%, B cell lymphoma (CSF more sensitive than serum)	CBA (CSF more sensitive than serum)
AK5	Limbic encephalitis	No associated tumour	CBA (sensitivity serum and CSF comparable)
IgLON5	Parasomnia, sleep apnoea, bulbar, PSP-like	Tumours rare, HLA-DRB1*10:01	CBA (serum more sensitive than CSF)
GFAP	Meningoencephalitis	<10%[e]	CBA (CSF more sensitive than serum)
GAD65	Limbic encephalitis, refractory epilepsy, stiff-person syndrome, cerebellar ataxia	<5%	ELISA (serum concentration relevant >10.000 IU/l; CSF concentration relevant >100 IU/l), CBA, RIA
MOG	Cortical encephalitis, optic neuritis, ADEM, myelitis	Rare	Flow cytometry (serum)

ADEM, acute disseminated encephalomyelitis; CBA, cell-based assay; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; IB, immunoblot; IF, immunofluorescence; MOG, myelin oligodendrocyte glycoprotein; NMDAR, *N*-methyl-D-aspartate receptor; PERM, progressive encephalopathy with rigidity and myoclonus; PSP, progressive supranuclear palsy; RIA, radioimmuno assay; SCLC, small cell lung carcinoma. [a]If commercially available, characteristics of the commercial test are provided. [b]If available, use a confirmational technique (usually tissue-based assay in antibodies against extracellular antigens). [c]Tr on IF–IB, DNER on CBA. [d]Sudden, brief, unilateral dystonic posture primarily affecting the arm and often the ipsilateral face[9] (a combination of peripheral nerve hyperexcitability, autonomic dysfunction and neuropsychiatric symptoms). [e]Excluding GFAP post-checkpoint inhibitors.

modulated by autoantibodies and some evidence also points to changes in NMDAR electrophysiology.

Understanding the precise mechanisms by which the autoantibodies cause disease can offer guidance in terms of probable effective therapies. For example, NMDAR antibodies act predominantly by acutely reducing channel function and internalization[92], with limited evidence supporting complement involvement[67]. Correspondingly, mouse models and retrospective human data have shown that drugs that modulate channel function and B cell depletion are effective therapies[5,93], whereas complement inhibition has not been explored. In diseases where protein–protein interactions are probably dominant the mechanisms of these autoantibodies (for example, those targeting LGI1 and CASPR2)[57,64,91,94], therapies that target these interacting domains or their downstream effects (such as AMPAR expression) may be effective interventions. More broadly, these autoantibody-mediated syndromes may be effectively treated with drugs that deplete IgG or tackle the underlying active B cell and plasma cell responses — these modalities are the subject of ongoing clinical trials[95]. Another translational avenue stemming from mechanistic understanding addresses antibody-mediated direct synaptic dysfunction. In vitro and in vivo

experiments have shown that small molecules binding to receptors can change their tertiary conformation (positive allosteric modulators). This conformation change can result in alterations that improve synaptic function via modifications in the cell-surface dynamics of receptors and partial antagonism of antibody-mediated internalization, quickly counteracting the autoantibody effects, which current immunotherapies are unable to do[88,90,96].

In summary, the specific autoantigen and its tissue and subcellular localization are major factors in the pathogenic mechanisms of AE. They directly or indirectly influence the clinical phenotype, course, immunological triggers, chronicity, reversibility and prognosis, relapse propensity and differential response to immunotherapy. These findings strongly support the categorization of AE subtypes according to the target autoantigen, for example, anti-NMDAR encephalitis. Ultimately, a thorough understanding of each pathogenic mechanisms underlying these diseases is not only essential for unravelling the pathophysiology but also for the exploitation of process-specific markers and the development of process-targeted therapies.

Diagnosis, screening and prevention

Diagnostic criteria

AE is clinically diagnosed based on the recognition of core symptoms. These symptoms include memory deficits, psychiatric symptoms such as psychosis, catatonia and behavioural changes, seizures, confusion and altered consciousness[12]. The manifestation of these symptoms can be acute, subacute or more chronic, and the duration of symptoms depends on the associated autoantibodies[12,97].

In 2016, consensus guidelines were published to accelerate and optimize the diagnosis and treatment of AE[12]. The diagnostic algorithm follows a three-step approach. The first step is possible AE or minimal requirements (symptoms and signs) to suspect AE in the acute clinical setting, which include acute or subacute onset (<3 months) of working memory deficits, altered mental state or psychiatric symptoms, together with at least one of the following criteria: new focal CNS symptom, new-onset seizures, CSF pleocytosis (>5/µl) and/or brain MRI suggestive of encephalitis (Table 3). Regardless of the level of evidence, it is crucial to exclude alternative diseases[15]. The second layer in the diagnostic work-up is probable AE including probable anti-NMDAR encephalitis[12]. If these criteria are met, commencing first-line immunotherapy is recommended before diagnosis is confirmed with antibody testing. In 2023, the criteria for probable anti-LGI1 encephalitis were suggested and validated[15] (Table 3). The third step in the diagnostic algorithm is definite AE, consisting of a typical clinical syndrome in combination with a positive antibody status.

Differential diagnoses

The differential diagnosis of AE is extensive and depends on the clinical symptoms and results from ancillary testing. Distinguishing AE from infectious encephalitis can be challenging in the early stages as clinical presentation and CSF findings can be similar. However, brain MRI can be helpful in such scenarios; for example, bilateral limbic T2/FLAIR hyperintensities are more common in AE than infectious encephalitis[22]. In every patient, comprehensive microbiological testing (blood and CSF) is required to exclude potential infectious causes and, in some cases, overlaps with rapidly progressive neurodegenerative conditions[98], metabolic disorders and genetic mimics should be considered[15]. Notably, a multicentre study published in 2023 described >100 patients misdiagnosed with AE. The most common alternative diagnoses were functional neurological disorders, neurodegenerative diseases, primary psychiatric diseases, cognitive deficits from comorbidities and

Table 3 | Diagnostic criteria for AE

Possible AE	Autoantibody-negative AE	Definite limbic encephalitis	Probable anti-LGI1 encephalitis	Probable anti-NMDA receptor encephalitis
Onset and symptoms				
Subacute onset (<3 months) of working memory deficits (short-term memory loss), altered mental status[a] or psychiatric symptoms			Subacute onset (<3 months) of memory deficits and of typical facio-brachial dystonic seizures or ≥5 (subtle) stereotypical focal seizures per day	Rapid onset of ≥4 of abnormal behaviour or cognitive dysfunction; speech dysfunction (mutism, verbal reduction, pressured speech); seizures; movement disorder, dyskinesias or rigidity; abnormal posturing; decreased level of consciousness; autonomic dysfunction or central hypoventilation
Diagnostic assessments				
≥1 of new focal CNS findings, new-onset seizures, CSF pleocytosis, MRI features suggestive of encephalitis[b]	Absence of autoantibodies in serum and CSF, and ≥2 of MRI abnormalities suggestive of AE[a]; CSF with pleocytosis or oligoclonal bands; brain biopsy showing inflammatory infiltrates and excluding other disorders	MRI showing bilateral brain abnormalities highly restricted to the medial temporal lobes and ≥1 of CSF with pleocytosis; EEG with epileptic or slow-wave activity involving the temporal lobes		≥1 of abnormal EEG (focal or diffuse slow or disorganized activity, epileptic activity or extreme delta brush); CSF with pleocytosis or oligoclonal bands
Reasonable exclusion of alternative causes: CNS infections, septic encephalopathy, metabolic encephalopathy, drug toxicity, cerebrovascular diseases, neoplastic disorders, Creutzfeldt–Jakob disease, epileptic disorders, rheumatological disorders, mitochondrial diseases, and additionally in children: Kleine–Levin, Reye syndrome, inborn errors of metabolism				

Diagnosis of an autoimmune encephalitis (AE) type can be made when all criteria for that type are met. CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalography; NMDAR, *N*-methyl-D-aspartate receptor. [a]Altered mental status defined as decreased or altered level of consciousness, lethargy or personality change. [b]Brain MRI hyperintense signal on T2-weighted fluid-attenuated inversion recovery sequences highly restricted to one or both medial temporal lobes (limbic encephalitis), or in multifocal areas involving grey matter, white matter or both compatible with demyelination or inflammation. Data from refs. 12,15.

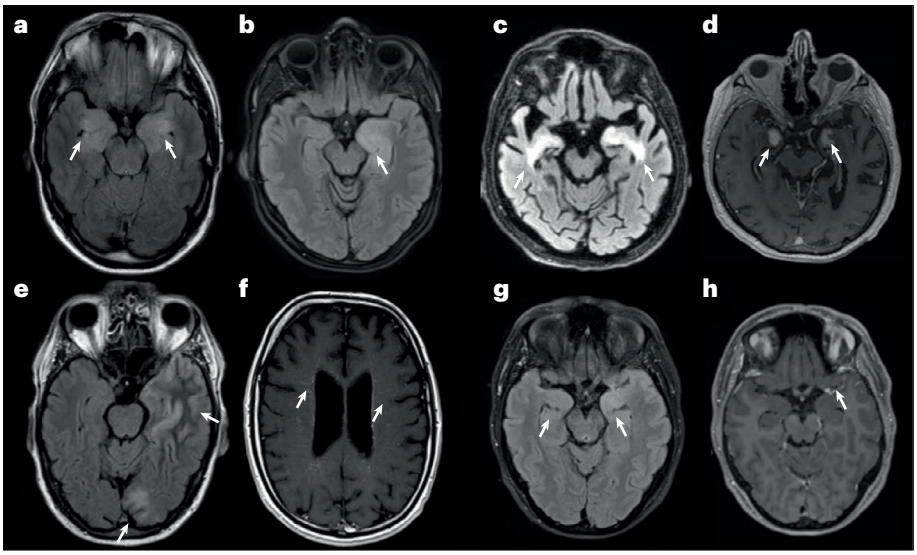

Fig. 4 | Typical MRI scans of patients with autoimmune encephalitis. **a**, The most typical MRI pattern is a bilateral hyperintense signal (arrows) on T2/fluid-attenuated inversion recovery (FLAIR) images in both mesial temporal lobes, defined as limbic encephalitis. **b**, A less common finding is unilateral hyperintensity (arrow) of the mesial temporal lobe on T2/FLAIR images. **c**, This T2/FLAIR image shows typical hyperintensity (arrows) at first glance, although it extends a bit too much beyond the mesiotemporal area. **d**, The contrast enhancement (arrows) on this T1 sequence is a red flag; this patient was diagnosed with neuro-Whipple. **e**, In anti-$GABA_A$ receptor encephalitis, multifocal, poorly demarcated, large white matter lesions (arrows) occur, as seen on this FLAIR sequence. **f**, In anti-GFAP astrocytopathy, a typical MRI feature is contrast-enhanced T1-weighted linear/radial perivascular enhancement (arrows). **g**, In the last patient, the T2/FLAIR images are typical for autoimmune encephalitis, showing bilateral hyperintensities (left more than right; arrows). **h**, The gadolinium enhancement (arrow) is atypical (red flag); the patient had a glioblastoma multiforme.

cerebral neoplasms[99]. Another study, describing >200 patients suspected of AE, also showed that AE mimics are frequent[15]. Red flags and contributors that should raise suspicion for an alternative diagnosis include an insidious onset of symptoms, the absence of MRI or CSF findings suggestive for neuroinflammation and the overinterpretation of nonspecific antibody test results[15,99,100].

However, in the 2016 guidelines, probable seronegative AE became a new entity[12]. This is a diagnosis based on the exclusion of other causes and the combination of well-defined criteria: acute or subacute onset (<3 months) of working memory deficits, altered mental state or psychiatric symptoms; absence of autoantibodies in serum and CSF; and at least two of the following criteria: mesiotemporal abnormalities on MRI (T2 or FLAIR), CSF abnormalities (pleocytosis, CSF-restricted oligoclonal bands or raised IgG index) and pathologically confirmed AE[101]. These criteria have since been applied successfully[102], and validated to be specific[15]. In the remaining patients fulfilling criteria of possible AE but without autoantibodies, it is important to exclude other causes[100]. The specificity of 'possible AE' (25%) is too low to allow it to be classified as a diagnosis[15].

One caveat is that several AE syndromes do not present subacute and take months to years to develop, and therefore they do not fulfil the criteria for this diagnostic algorithm[11]. This is mostly reflected in anti-IgLON5 and anti-CASPR2 diseases[97] and anti-GAD-associated syndromes. Additionally, especially in anti-LGI1 encephalitis, patients can also present with prominent seizures, but without fulminant encephalitis. Therefore, specific criteria to diagnose probable anti-LGI1 encephalitis have been created and validated[15]. Another caveat is that the algorithm should not be applied to patients without clinical features of encephalopathy (that is, working memory deficits, altered mental state or psychiatric symptoms), for example, the algorithm should not be used in cases of cerebellar symptoms, brainstem encephalitis or myelopathy.

Ancillary testing

Neuroimaging with brain MRI can reveal specific features of limbic encephalitis, including bilateral medial temporal lobe T2 or FLAIR hyperintensities[12,103]. However, unilateral medial temporal lobe T2 or FLAIR hyperintensities can be seen as well, yet are considerably less specific (Fig. 4). In ADEM and anti-$GABA_AR$ encephalitis, multifocal, poorly demarcated, large white matter lesions occur[104]. In MOGAD, AE signs of cortical encephalitis can be seen, with T2 or FLAIR focal hyperintensity and swelling in cortical regions[12]. Nevertheless, a normal brain MRI does not exclude AE. Conversely, some abnormal brain imaging findings can help to exclude other diagnosis such as HSV1 encephalitis, glioma, lymphoma, Creutzfeldt–Jakob disease and vasculitis, particularly, MRI abnormalities extending beyond the mesiotemporal lobes, contrast enhancement or diffusion restriction[15,99,105]. Longitudinal follow-up MRI assessments are clinically essential for confirming treatment responses, observing the resolution of previously observed T2 or FLAIR lesions, capturing the progression of brain atrophy indicative of unfavourable clinical outcomes[106], and for detecting recurrent, or new, brain lesions.

CSF analysis frequently shows pleocytosis or increased total protein. Intrathecal antibody synthesis, characterized by an elevated CSF IgG index or oligoclonal bands, is frequently associated with active immunopathogenesis within the CNS compartment[107]. Meanwhile, the prevalence of abnormal CSF findings varies depending on the associated autoantibodies; frequent in patients with anti-NMDAR encephalitis[5] and rare in those with LGI1, CASPR2 or IgLON5 antibodies[8,97]. Importantly, a normal routine CSF analysis is not uncommon in AE[11].

Electroencephalography frequently shows slowing or epileptiform discharges. Extreme delta brushes are a distinctive pattern seen in anti-NMDAR encephalitis[108], but only in a minority of mostly severely affected patients[109].

Fluorodeoxyglucose positron emission tomography (FDG–PET) is not part of the routine diagnostic work-up of most patients with possible AE. Although it is a sensitive tool, its specificity to distinguish AE from other neurological disorders is limited. FDG–PET can be used in patients with rapid progressive dementia to distinguish between an autoimmune or neurodegenerative aetiology. In anti-NMDAR encephalitis, FDG–PET can show frontal hypermetabolism and relative occipital hypometabolism[110,111].

Antibody testing

Autoantibody testing plays a crucial role in establishing a definite AE diagnosis. Sometimes, these autoantibodies may represent the only paraclinical finding indicating neuroinflammation, especially for patients with LGI1, CASPR2 and IgLON5 antibodies[8,10,97]. The different available neuronal antibody tests include commercially available kits, as well as in-house assays carried out only by experienced laboratories. The main techniques are tissue-based assays (indirect immunohistochemistry or immunofluorescence on rodent brain tissue), immunoblots, cell-based assays, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay and live hippocampal neurons.

A comprehensive evaluation of both serum and CSF specimens is essential to increase diagnostic accuracy[112]. In most commercial antibody tests, the specificity of CSF is higher than serum. For anti-NMDAR encephalitis, CSF is also more sensitive and specific than serum[11,113,114], and the same applies to GFAP antibodies[115]. However, in testing for LGI1 antibodies, sensitivity using widely used commercial test systems is higher in serum than in CSF[13,116]. Notably, different testing methods across the globe could be contributing to these variations and, in some countries, not all tests are available.

In interpreting test results, it is important to consider some issues. First, commercial kits carry a high risk of false-positive results, especially when testing serum only[112,117]. Therefore, antibody positivity should be confirmed by a second technique, preferably in a reference laboratory, especially when the clinical presentation does not match the known phenotype[100]. Second, low titre test results obtained through ELISA (GAD65)[118] often lack clinical relevance[119]. Importantly, some patients may exhibit the concomitant presence of multiple antibodies, as demonstrated by double positivity for anti-NMDAR and MOG-IgG[120,121] or GFAP and NMDAR[122].

Genetic testing

HLA analysis is not currently part of the routine diagnostic work-up of AE. However, studies have described associations with specific HLA subtypes and may be part of future management approaches. Examples include *HLA-DRB1*07:01* in ~90% of patients with anti-LGI1 encephalitis[28,29], *DRB1*11:01* in 48–94% of patients with anti-CASPR2 encephalitis[30,123], *DQB1*05:01* in ~85% of patients with anti-IgLON5 encephalitis[124] and *HLA-DQB1*02:01*/*HLA-DRB1*03:01* in 60–70% of patients with anti-Kelch-like protein 11 (KLHL11) encephalitis[125].

Tumour screening

In general, in patients with suspected paraneoplastic aetiology, tumour screening involves low-dose CT and contrast-enhanced CT of the abdomen and pelvis, accompanied by mammography or breast ultrasonography or MRI in women and testis ultrasound in men[16,126]. If screening is negative, usually PET–CT is performed[16,126]. However, FDG–PET is not a sensitive tool to screen for mature teratomas[126]. Pelvic MRI (preferentially 3T MRI with gadolineum), pelvic or transvaginal ultrasonography are sensitive modalities for detecting small ovarian teratomas in anti-NMDAR encephalitis[127]. In the absence of an initial cancer diagnosis, repeated screening every 3–6 months for a period of at least 2–5 years[128] is advisable for patients with high PNS Care scores, reflecting a high cancer risk[16]. This diagnostic score combines phenotype, antibody type and presence of a tumour (Table 4).

Management

The comprehensive management of AE requires both the rational use of available pharmacotherapeutics and a multidisciplinary team-based approach to holistic care throughout the often lengthy duration of the disease course. A comprehensive, multidisciplinary approach to care is needed to optimize recovery from AE. Beyond neurological care, many other specialties serve an integral role in diagnosing and treating AE, including psychiatry, critical care, paediatrics, oncology and rehabilitation medicine[129].

First, patients diagnosed with AE require rapid administration of empiric immunotherapies[130]. These should be initiated as soon as clinical suspicion permits a confident diagnosis, even without the results of specialized neural autoantibody testing. This enables early initiation of immunotherapy, which has been associated with improved neurological outcomes in the two most common forms of AE, anti-LGI1 encephalitis

Table 4 | PNS Care score

Assessment dimension	Criteria	Points
Clinical level[a]	High-risk phenotypes	3
	Intermediate-risk phenotypes	2
	Defined phenotype epidemiologically not associated with cancer	0
Laboratory level[b]	High-risk antibody (>70% cancer association)	3
	Intermediate-risk antibody (30–70%)	2
	Low-risk antibody (<30%) or negative	0
Cancer	Found, consistent with phenotype and (if present) antibody, or not consistent but antigen expression demonstrated[c]	4
	Not found (or not consistent), but follow-up <2 years	1
	Not found and follow-up ≥2 years	0
Diagnostic level	Definite ≥8	≥8
	Probable	6–7
	Possible	4–5
	Non-PNS	≤3

NMDAR, *N*-methyl-D-aspartate receptor; PNS, paraneoplastic neurological syndromes. [a]High-risk phenotypes: encephalomyelitis, limbic encephalitis, rapidly progressive cerebellar syndrome, opsoclonus-myoclonus, sensory neuronopathy, gastrointestinal pseudo-obstruction (enteric neuropathy), Lambert–Eaton myasthenic syndrome. Intermediate-risk phenotype: encephalitis, anti-NMDAR encephalitis, brainstem encephalitis, Morvan syndrome, myelopathy, stiff-person syndrome, polyradiculopathy. [b]High-risk antigens: Hu, CV2/CRMP5, amphiphysin, Ri, Yo, Ma1/Ma2, Tr/DNER, KLHL11. Intermediate-risk antigens: AMPAR, $GABA_B$ receptor, mGluR5, VGCC, NMDAR, CASPR2. Low-risk antigens: $GABA_A$ receptor, GFAP, GAD65, LGI1, DPPX, GlyR, mGluR1. [c]See Table 2. Reprinted from ref. 16, CC BY 4.0.

and anti-NMDAR encephalitis[5,12,14,15,131,132]. Of course, initiating therapy must be balanced against the substantial and established risks of misdiagnosis or over diagnosis[99]. These risks include infections and the opportunity to diagnose lymphomas or systemic inflammatory diseases.

Alongside immunotherapies, one important consideration is the effective and prompt treatment of tumours, when present. This intervention can help improve or stabilize some patients[133]. In addition to immunotherapies, other considerations include the use of symptomatic therapies including antiseizure medications, sedation for behavioural symptoms and drugs to treat movement disorders. In general, symptom therapies are far less effective than immunotherapies and are required at large doses before clinical effects are observed. Additionally, in particular, some antiseizure medications associate with substantial allergic reactions or behavioural adverse effects[9,30,134]. Together, owing to their limited efficacy combined with adverse effects, these therapies have a reduced priority in AE.

Immunotherapies

Early in the disease, immunotherapies can be categorized into two broad categories: first-line and second-line options.

Corticosteroids. Corticosteroids are generally initiated as soon as AE is strongly suspected. Corticosteroids exert broad anti-inflammatory effects, and are widely available[135] (Supplementary Table 2). In particular, in patients with anti-LGI1 encephalitis, seizure reduction is observed with this intervention alone, typically over just days to weeks. However, thereafter, these patients may be transitioned to oral prednisone per day to prevent relapses observed with rapid corticosteroid tapering[14]. By contrast, in patients with anti-NMDAR encephalitis, ~50% of patients improve within 4 weeks, so immunotherapy escalation is warranted in many cases[5,132,134]. The value of steroid sparing agents is driven by very limited available data. In many cases, especially severe cases, steroids are often combined with intravenous immunoglobulin and/or plasma exchange.

Plasma exchange. Plasma exchange is thought to remove circulating antibodies, immune complexes and cytokines[136]. The effect of plasma exchange can be apparent within just a few days. However, attributing improvements to any individual agent is challenging. Plasma exchange may be performed with central or peripheral venous access. Plasma exchange via peripheral venous access reduces two main risks: substantial haemorrhage and infection, and is simple to administer in agitated patients or patients with psychosis with AE[137].

Intravenous immunoglobulins. Intravenous immunoglobulin is postulated to exert its effect via one of several immunomodulatory functions including neutralizing autoantibodies and/or cytokines, saturating neonatal Fc receptors to decrease antibody recycling and inhibiting the complement cascade[138]. Intravenous immunoglobulin has been assessed in the only randomized controlled trial in AE. Although numbers were small and the effect was modest, intravenous immunoglobulin improved seizures and cognitive outcome compared with placebo[17].

Second-line and third-line immunotherapies

After first-line agents, attention is given to the degree of clinical improvement. So far, no biomarkers exist to supplement this assessment with a rational approach. The degree of improvement, the known trajectory of the individual disease and the consideration of relapse prevention guides the potential administration of second-line agents. Typically, these agents have been used in cases considered refractory or with unsatisfactory improvements, after first-line agents, mostly those with anti-NMDAR encephalitis. Second-line options include rituximab, cyclophosphamide and, to a lesser extent, tociluzimab, bortezomib, mycophenalate mofetil, azathioprine and maintenance intravenous immunoglobulin[130]. In the authors' experiences, the vast majority of cases only receive rituximab or cyclophosphamide. Additionally, many novel, emerging medications have been studied in smaller numbers. These include complement inhibiting therapies, anti-CD38 monoclonals, BAFF/APRIL inhibitors, calcineurin inhibitors, integrin inhibitors and JAK inhibitors (Fig. 5).

B cell-targeting therapies. B cells differentiate into antibody-secreting cells, present antigens to activate T cells and secrete a variety of signalling molecules[139]. The ability to use monoclonal antibodies to deplete B cells, by exploiting B cell-restricted surface markers such as CD20 and CD19, provides an opportunity to potentially target all these roles, and offers options in a broad range of diseases. Although CD19 is expressed on a wider B cell lineage, from pro-B cell to some plasma cells, the direct role of $CD19^{+}CD20^{-}$ antibody-secreting cells in autoantibody-mediated diseases remains uncertain[61,140]. As CD20 therapies (that is, rituximab) do not substantially reduce autoantibody levels, it has been proposed that they work by termination of human germinal centre reactions, which seem important to the propagation of many of these diseases[46,58]. Each CD20 and CD19 depleter has distinctive target epitopes and binding affinities, with consequently differing mechanisms of B cell depletion. These drugs also differ in immunogenicity and frequency of infusion-related reactions[141], but no head-to-head comparisons between these agents limits the ability to make specific recommendations. Nevertheless, rituximab is currently the only medication in this class to be included in the WHO Model List of Essential Medicines, making it the most accessible worldwide. Meta-analyses of patients with AE, NMOSD and paediatric CNS inflammatory disorders show promising results for rituximab therapy[142–145]. In anti-NMDAR encephalitis, rituximab is associated with better outcomes, defined as a reduction in the modified Rankin Scale (mRS)[146] and mortality, versus administration of no second-line therapies[5]. The largest study of rituximab in AE has shown no clear benefit in the acute treatment of patients with anti-LGI1 encephalitis and anti-GAD65 encephalitis[77], although this study was not powered nor designed to identify an effect.

Inebilizumab is the only monoclonal antibody in the CD19 subclass studied in neurological disease. Inebilizumab is FDA approved for the treatment of NMOSD[147], and an ongoing clinical trial in anti-NMDAR encephalitis (the ExTINGUISH Trial)[148] will inform its role in AE. Its mechanism of action may be very similar to anti-CD20 therapies, although only small autoantibody reductions have been observed[149].

Both rituximab and inebilizumab deplete peripheral B cells for ~6–9 months. Regular dosing upon B cell reconstitution enhances compliance but increases risks of infections and can render some patients hypogammaglobulinaemic[150]. In particular, data from patients with multiple sclerosis suggest a particularly steep rise in infections after rituximab[150], which is of relevance to the several late-onset forms of AE, for example, those associated with antibodies to LGI1, CASPR2 and IgLON5.

In addition, cellular B cell-depleting therapies (that is, chimeric antigen receptor-T cell therapies) are an emerging field. Data in AE and related neurological diseases are limited[151,152], but the striking and

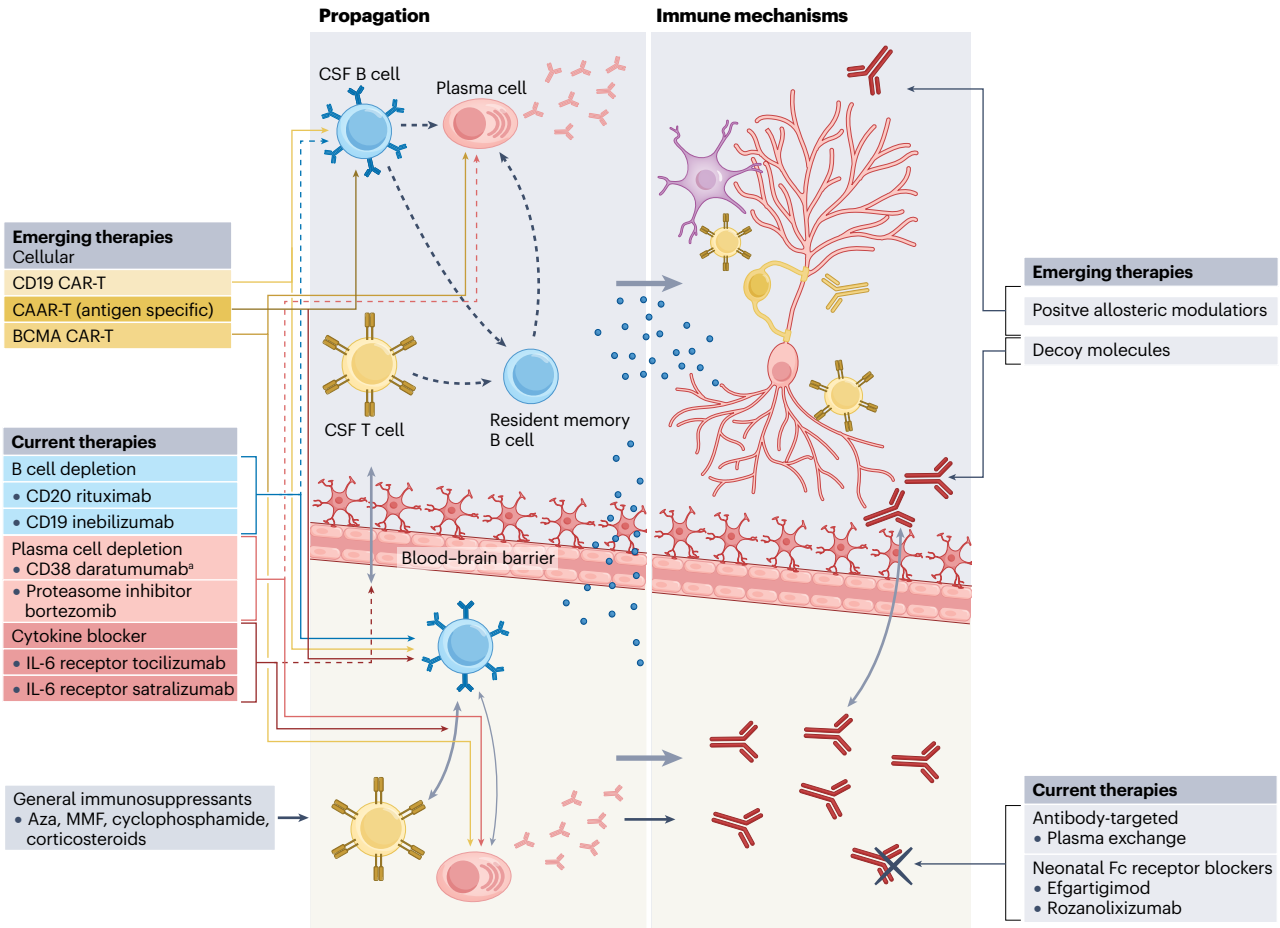

Fig. 5 | Second-line immunotherapies in autoimmune encephalitis. The pathophysiological targets and pathways relevant in autoimmune encephalitis are shown. BCMA, B cell maturation antigen; CAAR, chimeric autoantibody receptor; CAR, chimeric antigen receptor; CSF, cerebrospinal fluid; MMF, mycophenolate mofetil. [a]Daratumumab depletes plasmablasts and plasma cells but also natural killer cells, effector and regulatory B cells and T cells, and is therefore a broader-acting biological.

durable results in drug refractory lupus and systemic sclerosis cases has garnered enthusiasm for this approach[153].

Inhibitors of DNA synthesis. Inhibition of DNA synthesis unselectively results in the death of rapidly dividing cells. Many classical chemotherapeutic agents fall into this class. These medications are associated with toxicity at high doses, but adverse effects are limited at lower doses[130].

Cyclophosphamide is a cytotoxic alkylating agent with specific sensitivity to haematopoietic cells such as B cells and T cells. Outside of oncology indications, this broad lymphocyte targeting, in addition to its crossing of the blood–brain barrier, has made it a valuable second-line treatment in autoimmune neurologic disorders[5,154]. Although affordable and with a relatively rapid onset, adverse effects include myelosuppression, bladder toxicity, gonadal toxicity and subsequent malignancy. However, these effects are especially related to its chronic use[155] and cumulative doses much higher than those reached in acute AE treatment.

Two other commonly used agents that disrupt DNA synthesis are azathioprine and mycophenolate mofetil. Both agents inhibit key pathways of cell division, purine metabolism and adenosine monophosphate dehydrogenase, respectively, to which frequently dividing lymphocytes are especially sensitive. Azathioprine has been used as second-line immunotherapy in AE cases with different antibodies, and mycophenolate mofetil less frequently, but has been suggested to prevent relapses in patients with anti-LGI1 encephalitis[156]. However, a major drawback of either agent is that a perceptible clinical benefit can take several months to achieve, which probably limits its use exclusively to potential steroid sparing agents in reducing relapse rates, as these can be as high as 40% in some patient groups.

Cytokine antagonists. Cytokines exert a wide variety of immunological effects, including the development and coordination of innate and adaptive immune responses[157]. Hence, cytokine antagonists are used to treat various systemic inflammatory and autoimmune conditions. The most relevant targeted cytokine in AE is IL-6, which is a highly pleotropic pro-inflammatory cytokine that promotes B cell survival, stimulates antibody production, supports helper T cell proliferation and decreases blood–brain barrier dysfunction[158,159]. IL-6R targeted monoclonal antibodies disrupting this pathway include tocilizumab and satralizumab. In retrospective

series, the staged 'T-SIRT' approach (teratoma–steroids–intravenous immunoglobulin–rituximab[150]–tociluzimab) has been reported to decrease the mRS in patients with anti-NMDAR encephalitis[127], although many were treated very early with tocilizumab. In NMOSD, satralizumab has been shown to be effective in reducing relapses[160,161]. The CIELO clinical trial[162] is currently recruiting to investigate the safety and efficacy of satralizumab in anti-NMDAR encephalitis and anti-LGI1 encephalitis.

Neonatal FcRn inhibiting therapies. The neonatal Fc receptor (FcRn) is widely expressed, including on endothelial cells and, at this site, extends the half-life of immunoglobulins by endocytosing antibodies and preventing their degradation in circulation[163]. FcRn blockade results in a notable reduction of circulating IgG levels, often to 30% of baseline[164]. Hence, unlike CD20- or CD19-depleting therapies, these drop IgG levels. However, akin to B cell depleters, they lack selectivity for the pathogenic autoantibodies.

Rozanolixizumab is an FcRn-directed monoclonal antibody now approved for the treatment of anti-AChR myasthenia gravis, as well as patients with anti-MuSK and myasthenia gravis; randomized controlled trials are also investigating its use for MOGAD[156,165].

Proteasome inhibitors. Inhibitors of proteasome subunits prevent protein degradation, leading to the accumulation of toxic protein species, with subsequent cell death. As plasma cells have an especially high production of their key secreted proteins (antibodies), they are relatively susceptible to these drugs. There are case reports of patients with treatment-refractory anti-NMDAR encephalitis that suggest a possible benefit of bortezomib[166–169]. The Generate-Boost clinical trial is currently investigating its role in refractory AE[170]. However, its poor CNS penetration and lack of effect on CSF-enriched plasmablasts may limit this approach[61,171].

Quality of life

Patients post-AE can experience a range of outcomes, with neural antibody type and the underlying pathophysiology contributing to heterogeneity. Clinical relapses are observed in 12–35% of patients[172], and mortality can range between 5% and 40% depending on the aetiology and disease severity[5,7,173]. Disability is often measured using the mRS, and long-term disability can be influenced by neural antibody type, immunosuppression, severity (including intensive care admission) and duration of follow-up. In a large cohort of patients with anti-NMDAR encephalitis followed for 24 months, 81% had a good mRS (0–2)[5]. AE associated with high-risk paraneoplastic antibodies often have worse outcomes in terms of disability and mortality than those with autoantibodies against extracellular epitopes[125,174].

The contemporary recognition of AE implies limited longitudinal data and AE-specific outcome measures. The mRS may fail to capture AE-specific longitudinal symptoms[175]. Patients post-AE often experience cognitive dysfunction and fatigue, sleep and mood disorders[176] that may not appear for months to years[47,177–179]. The clinical assessment scale in AE (CASE) was designed to accurately grade disease severity in AE. This scale is a composite score including seizures, memory dysfunction, psychiatric symptoms, level of consciousness, language problems, movement disorders, gait instability and ataxia, brainstem dysfunction and weakness. This score correlates well with mRS; however, as it was developed in a cohort enriched with patients with anti-NMDAR encephalitis, it may not fully capture symptoms in other encephalitis cohorts[180,181]. Further, owing to its aggregate structure, it may not capture detailed cognitive and mood symptoms (ceiling effect) and may be most useful in acute and subacute settings.

Cognitive impairment can be objectively evaluated with screening tools and neuropsychological testing. After anti-NMDAR encephalitis, several cognitive domains can be affected[182–186]. The frequency depends on age, neuronal antibodies, comorbidities and the test batteries used. Psychiatric symptoms such as psychosis and mania are frequent in the acute phase of anti-NMDAR encephalitis[4,187,188]. Long-term psychological symptoms are frequent, including depression and anxiety, and may impact quality of life and contribute to other symptoms such as cognition[176]. In anti-LGI1 encephalitis, cognitive deficits and REM sleep behaviour disorders have also been observed frequently after the acute disease[189].

Seizures are frequent at the onset of AE, but the incidence of long-term epilepsy is more limited. In patients with AE and intracellular antibodies, structural brain damage is common and the risk of developing epilepsy is higher than in patients with cell-surface antibodies[134,190–192]. The risk of developing epilepsy after anti-LGI1 encephalitis varies between 3% and 25%[14,134,193–196]. There are caveats interpreting these data such as the inclusion of relapses, selection bias for refractory cases and underdiagnosis of subclinical seizures, but in the authors' experience, the most accurate frequency is <10%.

Global function and quality of life can be impacted by AE. In a longitudinal study of patients with anti-NMDAR encephalitis, 50% were unable to return to work, use transport or travel in their communities, with nearly 50% unable to manage their finances[197,198]. Among a cohort of patients with anti-LGI1 encephalitis, only 15% returned to their pre-morbid role and many reported fatigue as a residual symptom[179]. Indeed, in this condition, residual fatigue is the main predictor of quality of life. Quality of life, including residual fatigue, have also been captured in the LGI1-specific patient-reported outcome measure (LANTERN)[199] or the AE-specific PROSE[200].

Outlook

AE is a well-described, treatable neuro-inflammatory condition. The incidence of AE has increased owing to better recognition of symptoms and signs, and the optimization of laboratory techniques. Good international collaboration, essential in rare diseases, has contributed to these improvements. Important achievements are the diagnostic guidelines published in 2016 and 2021 (refs. 12,16). These guidelines contain well-defined criteria that help clinicians in deciding when to include AE in the differential diagnosis in the acute setting (possible AE), when to start immunotherapy before antibody results return (probable AE), when to make a definite diagnosis (definite AE), and how to rate and identify paraneoplastic syndromes and associated tumours. In addition to better recognition of AE, more attention has been paid to diagnostic pitfalls[100]. Prior studies have focused on describing characteristics that occur more in AE than in alternative diagnoses and vice versa, and also on optimizing antibody assays. Examples are clinical prediction tools to use in patients with prominent seizures or focal epilepsy (that is, the Antibody Prevalence in Epilepsy (APE2) score[201] and the Antibodies Contributing to Focal Epilepsy Signs and Symptoms (ACES) score[202]), the description of typical and atypical MRI findings and the rise in biomarker research (that is, neurofilament light-chain levels in patients with psychiatric symptoms[203]).

With this knowledge, we are able to identify those patients that require immunotherapy. However, which treatment that patient needs to achieve optimal outcomes is the next important question to

enable. This patient-tailored treatment will depend on specific patient characteristics and disease signs.

Thus, current research focuses on the study of antibody effects, optimizing AE outcome measures and prediction tools, comparing different treatment protocols, and assessing the beneficial and adverse effects of new treatments. The vast and rapid expansion of platforms to investigate expression by and the effects of single cells in tissue, CSF and blood of patients with AE before and after treatment will improve our understanding of the pathophysiological mechanisms in AE. The large amount of data generated will necessitate active collaboration between researchers across the globe to provide sufficient statistical power for these analyses. Despite the continued discovery of antibodies present in patients with AE, the latest findings have proven more difficult to reach the mainstream diagnostic process or have failed in confirmation beyond initial publications. Hence, new ways of antibody discovery relevant to clinical practice are needed.

In AE treatment, therapeutic approaches remain largely empiric. Research efforts should focus on identifying factors to stratify patients and undertaking trials of rationale immunotherapy. In some types of AE, such as anti-NMDAR or anti-LGI1 encephalitis, randomized controlled clinical trials seek to provide evidence to support treatment decisions in the future. The challenge lies in recruiting enough patients to obtain meaningful results; the success of these trials and others will depend on neurologists and patients worldwide recognizing that evidence-based treatment guidance requires participation and inclusion in randomized controlled trials. In addition, the current complexity of trials[95], as well as the excessive costs and time efforts, limit progress in the field of medicine, and even more in rare diseases such as AE. Thus, creative solutions to compare treatment strategies in patients will be needed. Robustness to ascertain the effects and safety of therapies will still be required, but also calls for flexibility of medicine agencies to allow evidence beyond that from randomized controlled trials.

In addition to immunotherapeutics, treatments for symptoms in both the acute phase of AE and thereafter are needed. This includes conditions such as fatigue, pain, social isolation, persistent cognitive deficits, epilepsy, depression and anxiety, to maximize clinical recovery.

Furthermore, interest in the multitude of AE sequelae other than relapse is increasing. Thus, it will be useful to consider multidisciplinary approaches that include rehabilitation medicine, mental health care, social workers and other specialists, asking both patients and caregivers for other symptoms, considering a more extensive checklist and enabling holistic treatment. To determine which treatment is best, creating a robust and pragmatic AE outcome measurement tool that encompasses the full trajectory of illness (acute, post-acute and chronic) is essential. Research is needed to develop and validate AE-specific longitudinal outcome measures including standardized neuropsychological test batteries, mood (particularly anxiety and depression) scales and patient-reported outcome measures.

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Additional information

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